# Dose dependence: toxins & nutrients

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## Dose-dependence

You may have heard the phrase, "the dose makes the poison." Attributed to Paracelcus[1], this maxim expresses a basic principle in toxicology that negative effects increase with the amount or concentration of some potentially harmful substance[2]. A staple experiment in toxicology is thus, not surprisingly, the *dose-response* experiment in which groups of organisms are exposed to one of a series of increasing doses of the chemical of interest, usually spanning several orders of magnitude, and the outcome (e.g., death) is observed. Usually there is some sort of sigmoidal (S-shaped) relationship where nothing much happens at low doses and the response increases to a virtual certainty at high enough doses. Note that this relationship is usually sigmoidal only on a logarithmic x-axis. Doubling the dose does not double the probability of a response, but increasing the dose 10-fold might.

On the right is an actual dose-response curve involving guinea pigs from Savransky et al. 2013 as a random example.

There is something puzzling about this sigmoidal relationship. After all, isn't there simply some lethal dose that can be survived and then anything below that is, at least under good conditions, survivable? And why does the curve taper off slowly when it reaches the maximum? Why does it not just hit the 100% mark quickly? We can find a sort of answer to both questions by considering the fact that individuals are not all identical.

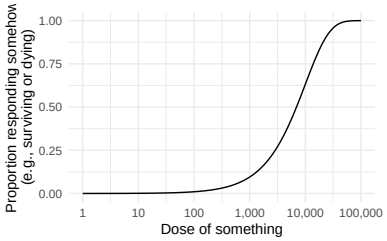


Figure 1: A hypothetical dose response.

[1] "All things are poison, and nothing is without poison, the dosage alone makes it so a thing is not a poison." -Paracelsus

[2] And the reverse is also true. The dose also makes the cure!

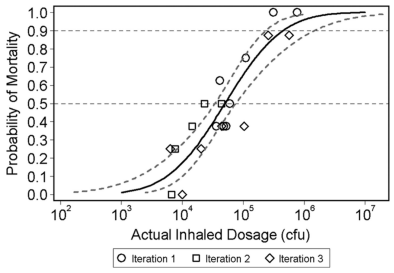


Figure 2: The proportion of guinea pigs that died with increasing doses of anthrax spores. (I couldn't find an example with toxins. Indeed, gunea pigs were more often used in immunology than toxicology. And anyway, mice and rats are the real "guinea pigs" these days, anyway.)

### The tolerance model and heterogeneity in susceptibility

Let's begin with this assumption, that hosts (i.e., individual animals) vary in the amount of the toxin[3] it can survive. Perhaps this is because of difference in activity in their liver (if they have a liver) or efficiency of their detoxifying enzymes or just plain "vigor"[4]. This results in what is called a tolerance model, which has its origins in calculating effective doses of insecticides. In this context the idea is that an individual can tolerate a given amount of the insecticide, but succumbs beyond that. Hence the term "tolerance" model.

Let us assume that the population (e.g., of guinea pigs[5]) has a distribution of tolerances to, say, Roundup, a glyphosate-based herbicide. Let's further assume that this distribution is a normal bell-shaped curve with a mean of $\mu$ (a concentration Roundup on the log-10 scale) and a standard deviation of $\sigma$. This means that half the population can withstand just under $\mu$, let's say mg/g, without becoming sick and dying. This half-way point should correspond to the $LD_{50}$, the dose at which half the population is expected to die. At lower doses, the threshold amount of Roundup has not been exceed for nearly as many guinea pigs, but

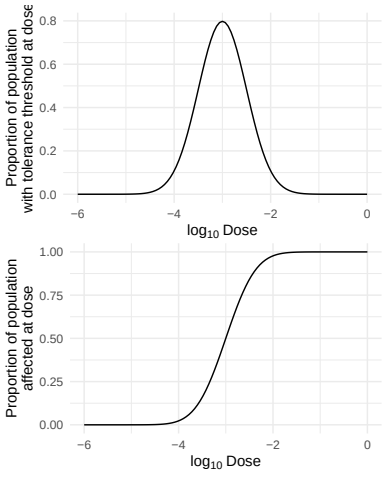


Figure 3: A hypothetical distribution of tolerances in a group of animals (top) and the proportion of the group that would be affected (i.e., die) if exposed to a given dose (bottom).

[3] Or toxicant, if it is abiotic in origin.

[4] Whatever that means.

[5] Can you imagine a herd of wild guinea pigs? Well, cavy. Either way, it would be rediculously cute!

at higher doses the threshold is exceeded for most guinea pigs. Hence, we get a classic, sigmoidal dose-response.

Now let us imagine that we study two populations og guinea pigs the same *average* tolerance (or resistance) to Roundup. The first is an inbred group of animals that are more alike, and thus less variable (smaller $\sigma$) while the second is a wild population of outbred animals that has much more variation among individuals (larger $\sigma$). As you would expect, the tolerance distribution for the wild population is wider than that of the inbred population, but as you might not have expected, you can actually see the outcome in a dose-response experiment. The wider distribution of tolerances results in a less-steep sigmoidal curve. Why is that? Hint, pick a point on the x-axis (e.g., -4), and think about what fraction of each population would succumb. Then pick another (e.g., -2) and repeat.

So dose-response experiments tell us about the average response, as well as the distribution of responses. That is, it can tell us about the heterogeneity in susceptibility. This is cool in its own right[6], but it also tells us something important: over a sometimes wide range of concentrations of a toxin, there will *usually* be some survivors. This is important because, assuming tolerance is heritable, these survivors can go on to reproduce and make a more tolerant population overall. Evolution by natural selection in action!

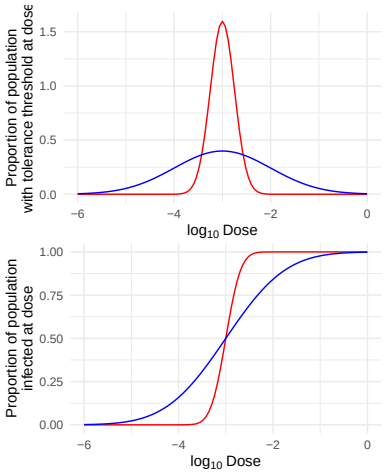


Figure 4: Tolerance distributions (top) and proportion that die at a given dose (bottom) for a highly inbred (red) and a more variable, outbred (blue) population.

[6] And if we switch from thinking about toxins to infections, this can tell us something about how disease moves through or is transmitted in a population!

## The other end of the spectrum

Of course not all chemicals are toxic (at least not at lower doses), and some are essential for growth, replication, and overall health. We can take the same sort of approach, but change the response from "death" to, say, "reproduction." The tolerance distribution becomes the distribution of nutrient $x$ required reproduce[7]. We get the same sort of sigmoidal response, only we would be happy to see that response.

When we step away from binary responses (do or do not reproduce) to quantitative responses (e.g., growth rates) is that we can observe a dose-response relationship even within an individual or among identical individuals. If growth is being slowed by a iron deficiency, adding a bit of iron will spur a bit of growth, but adding more iron will, perhaps, spur even more growth. The dose-response helps describe the case where, eventually, the benefits of additional iron, or any other no longer-limiting nutrient, wane.

Think, too, about the steepness of the dose-response curve. If it is steep, then there is only a narrow range of doses where you will actually see a response (e.g., increased growth), meaning you tend to have either too little or more than enough. What would that mean for, say, the efficacy of a fertilizer or nutritional supplement? Contrast that with a shallow dose-response curve. Now I'll be honest, I really don't know the shape of the dose-responses of any nutrients, but I suspect that most are fairly steep and thus there are probably rare occasions where supplemental nutrients help[8].

[7] One detail I'm sweeping under the rug is the difference between acute, all-at-once dosing as opposed to the intake rate over a longer period of time. This is on purpose. These distinctions are complicated by residence times and capacity to accumulate, but do not change the overall message I'm trying to convey.

[8] And I can say from experience that iron supplements stain the ceiling when spit out by one's less than enthusiastic toddler. So there are costs to nutritional supplements as well as possible benefits.